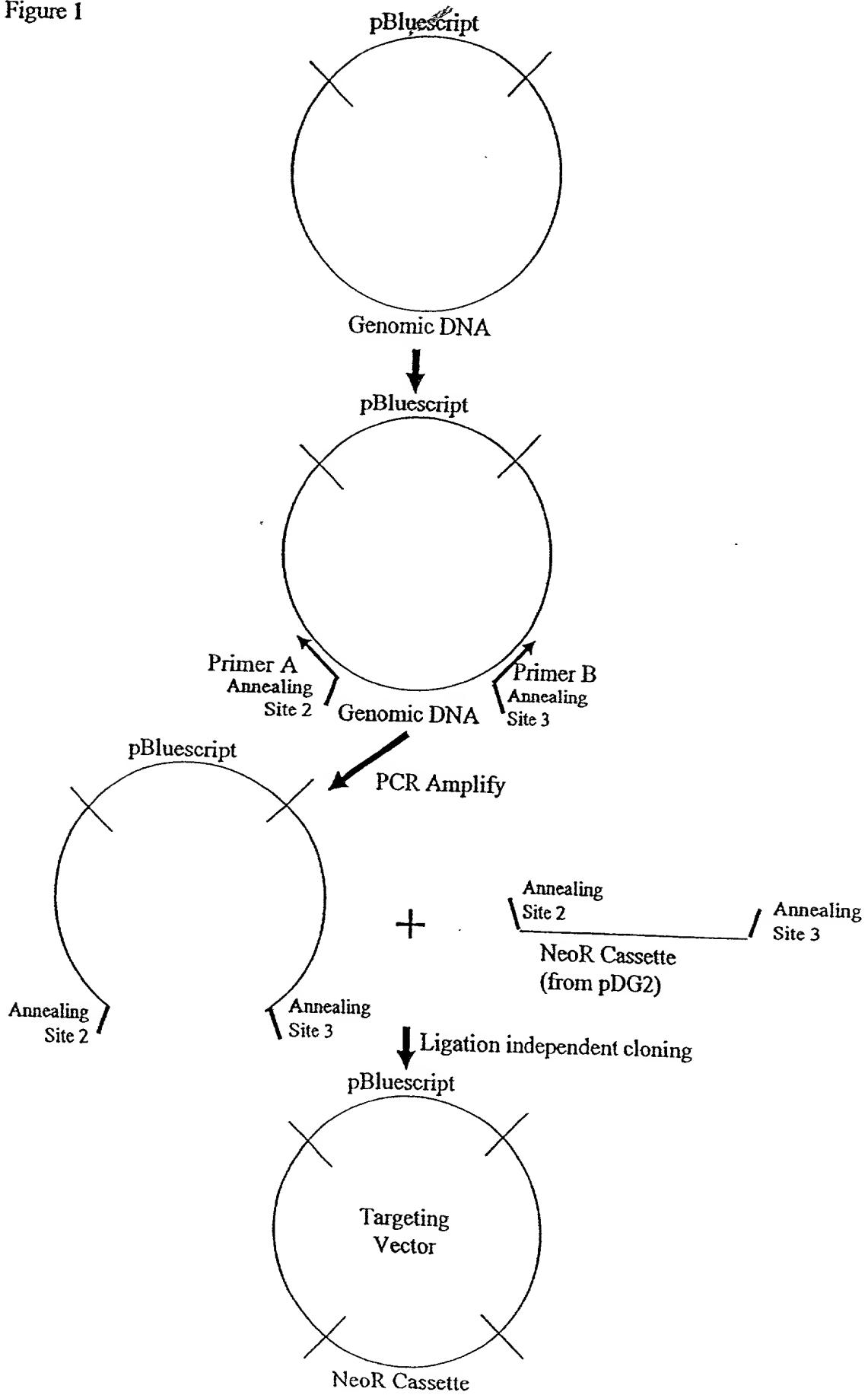
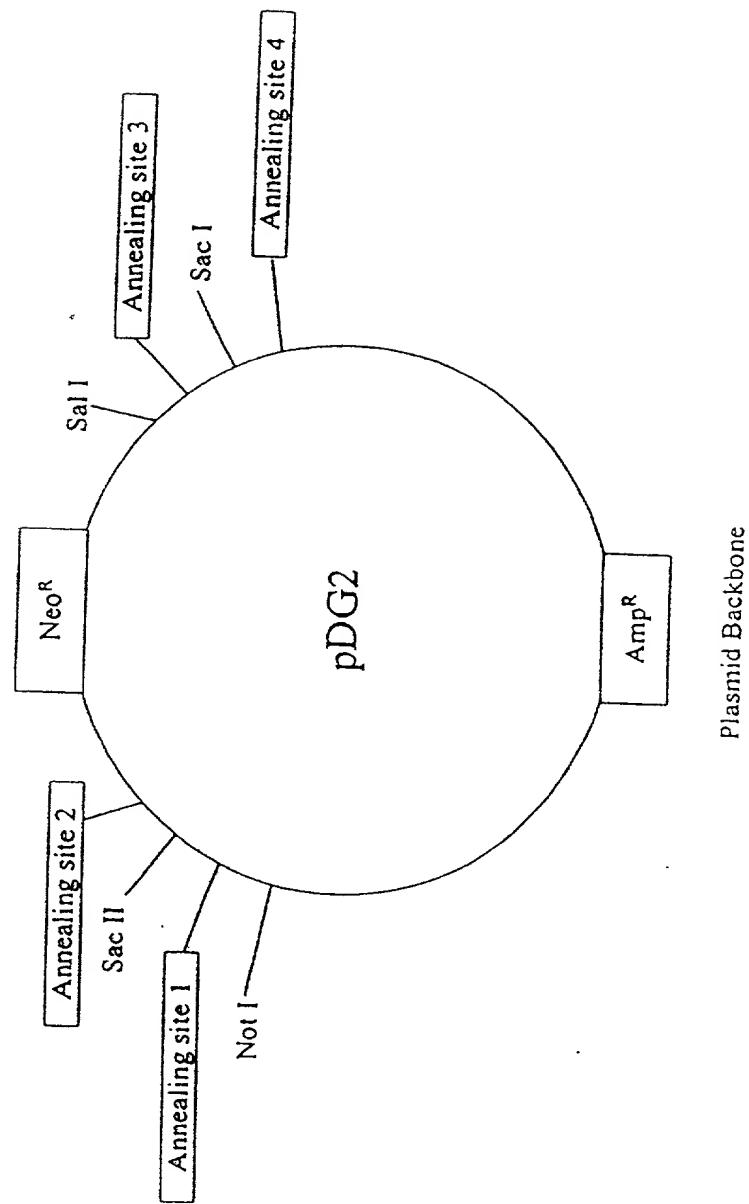


Figure 1





Plasmid Backbone

FIGURE 2A

FIGURE 2B

pDG2:

GTAACTACGTCAAGTGGCACTTTGGGAAATGTGGCGGAACCCCTATTTGTTATTTCTAAATACATTCAAATA
TGTATCCGCTATGAGACAATAACCCCTATAAATGCTCAATAATATTGAAAAGGAAGAGTATGAGTATTCAACATT
CGTGTGCCCTTATCCCTTTTGGCGCATTTGCCCTCTGTTTGCACCCAGAAACCGCTGGTGAAGCTAAAGA
TGCTGAAGATCAGTGGGTGCACGAGTGGGTTACATGAACTGGATCTCACAGCGTAAGATCCTTGAGAGTTTGC
CCGAAGAACGTTCCAATGATGAGCACTTTAAAGTCTGCTATGTTGCGCGTATTATCCGTGTTGACGCCGGCAA
GAGCAACTCGTCGGCATACTATTCTAGAATGACTTGGTGAAGTACTCACAGAGTACAGAAAAGCATCTTACCGA
TGGCATGACAGTAAGAGAATTATGCACTGCTGCCATAACCATGAGTGAACACTCGGCCAACTTACTTGACAAACGA
TCGGAGGACCGAAGGAGCTAACCGCTTTTGACAAACATGGGGATCATGTAACCTGCCCTGATCGTGGGAACCGAG
CTGAATGAAAGCCATACCAAACGAGCGTGAACCCAGATGCCGTAGCAATGCCAAACAGTGGCACAACATTAAAC
TGGCAACTACTTACTCTAGCTTCCCGCAACAAATTATAGACTCGATGGAGGGGATAAAGTGCAGGACCAACTCTGC
GCTCGGCCCTCCGGCTGGCTGGTTATTGCTGATAAATCTGGAGCGGTAGCGTGGGTCTGCCGTATATTGACGA
CTGGGCCAGGGTAAGCCTCCGCTGTTATCTACAGCGGGAGCTAGGCCAACTATGGATGAACGAAATAG
ACAGATCGCTGAGATAGGTGCTCACTGATTAAGCATGGTAACCTGAGACCAAGTTACTCATATAACTTTAGATTG
ATTACCCCGTTGATAATCAGAAAAGCCCAAAACAGGAAGATTGATAAAGCAAATATTAAATTGAAACGTTAATA
TTTGTAAAATCGCTTAAATTGTTAAATCAGCTATTAAACCAATAGGCCAAATCGGCAAAATCCCTTAA
AAATCAAAAGAATAGCCGAGATAGGGTGAGTGTGTTCCAGTTGGAAACAGAGTCCACTATTAAAGAACGTTGACTC
CAACGTCAAAGGGCAAAACCGCTATCAGGGCGATGGCCCACTACGTGAACCATCACCAAATCAAGTTTGGGT
CGAGGTGCGTAAGCCTAAAGGAGCCCTAAAGGGAGCCCGATTAGCTGACGGGAAAGCGAACGTC
GAAAGGAAGGAAAGGAAAGCGAAAGGAGCGGGCTAGGGCGTGGCAAGTGTAGCGGTACGCTGCGCTAACACCA
CCCGCGCGCTTAATGCGCGCTACAGGGCGCTAAAGGATCTAGGTGAAGATCTTTGATAATCTCATGACCAAA
TCCCTTAACGTGAGTTTCTGCTCACTGAGCGTCAAGGCCCTAGAAAAGATCAAGGATCTCTTGAGATCTTTT
CTGCGCTTAACGTGCTGCTGCAACAAAAAAACCCGCTACCGGGTGGTTGCGGTACAGAGCTACCAAC
TCTTTTCCGAGGTAACGCTTACGGCTACAGAGCGAGTACCCAAATGTTCTCTAGTGTAGCCGTAAGGGCAC
ACTTCAAGAAACTCTGAGCCCTACACCTCGCTGTAATCTGTTACAGTGGCTGCTGCAAGGGGATAAAG
TCGTGTCTTACGGGTTGACTCAAGACGATAGTTACGGATAAGGGCAGGGTGGCTGAAACGGGGGTTGTGAC
ACAGCCCAGTTGGAGCGAACGACCTACACCGAAGTACCTACAGCGTGAAGCTATGAGAAAGGCCACGCTTCC
AAGGGAGAAAGGCCACGGTATCCGTAAGGGCAGGGTGGAAACAGGAGAGGCCACGAGGGGCTTCCAGGGGAAAC
GCCTGGTATTTAGTCTGCTGGGTTGCCACCTCTGACTTGAGCGTCATTGATGCTGTCAGGGGGCG
GAGCCTATGAAAACGCCAGCAACGCCCTTTACGTTCTGCCCTTGTGGCTTGTACATGTAATGT
AGTTAGCTCACTTACGGCAGCCCTTACACTTATGCTTCCGCTGATGTTGTGGAATTGTGAGCGGATA
ACAATTACACAGGAAACAGCTATGACCATGATGCCAAGCTACGTAACGACTCACTAGCGGGCGCTTAAAC
AATGTCCTCTTGGCTGCTCCGGGCAACAGGAGCAAGAACAGCTGCAAGCTCCGGGACCGCTG
AGCGGGCGCGAATTCTGCAAGGATTCTGAGGGCCCTGCAAGTCATTCTACGGGCTAGGGGAGGCCCTTCCAAGG
CAGTCTGGAGCATGCCCTTAGCAGGCCCTGCACTGGCGTACACAAGTGGCTCTGCCCTGACACATTCCACA
TCCACCGGTAGGCCAACCGCTCCGTTTTGGTGGGCCCTCGGCCACCTTCTACTCCTCCCTAGTCAGGAAGTC
CCCCCGCCCGCAGCTCGCTGCAAGACGTGACAATGGAGTAGCACGTCCTACTAGTCCTGCAAGTGGACAG
CACCGCTGAGCAATGGAGCGGTAGGCCCTGGGCAAGCGGCCAATGCACTTCTCCCTGCCCTTGTGGCTCAGA
GGCTGGGAAGGGGGGGTGGGCCGGGCTCAGGGGGGGCTCAGGGGGGGGGCGGAAGTCTCTCCAGGGGCC
GGCATCTCGCACGCTTCAAAAGCGCACGCTGCGCGCTGTTCTCTCATCTCCGGCTTGTGACCTGAGC
CAATATGGGATGCCATTGAACAAGATGGATTGACCGAGTCTCCGGCGCTGGGGGAGAGCTATTGGCTATG
ACTGGGCACAACAGACAATCGCTGCTGATGCCCGTGTCCGGCTGTCAGCGCAGGGCGCCGGTTCTTGT
AAGACCGACCTGTCGGTGCCTGAATGAACTGCAAGGAGGAGCGCAGGCCCTGTCAGGCCACGGGCTTCC
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GGCCGGCTGGGTGCGGACCGCTATCGAGACATAGCGTTGCTACCCCTGATATTGCAAGAGCTGGCGGAATG
GGCTGACCGCTTCTCGTGTACGGTATGCCGCTCCGATCGCAGGGCATGCCCTTATGCCCTTGTGACGGAGT
TCTCTGAGGGGATGATCGCTCTGTAAGTGTGAGAAATTGATGATCTATTAAACAAATAGTGTGCAAGTT
AAGTTTTCTGTCATACTTTGTTAAGAAGGGTGAGAACAGAGTACCTACATTGAAATGGAAGGAGTGGAGCTACGGG
GTGGGGGTGGGGGGGATTAGATAATGCTGCTTTACTGAAGGCTTTACTATTGCTTATGATAATGTTCTAG
TTGGATATCATAATTAAACAGAAAACAAATTAGGGCAGCTATTCTCCACTCATGATCTAGATCTATAGA
TCTCTGTTGGGATATTGTTCTTGTGATCCCACATTGTTGTTCTAAGTACTGTGTTCCAAATGTCAGTTCA
TAGCTGAGAACGAGATCAGCACCTCTGTTCCACATACACTTCACTTCTAGTATTGTTGCAAGTCTAATTCCAT
CAGAACGACTAGATCTGAGTCCGGCCACCTAGGCCCTGACCTGAGTCAAGTACCAAGGCTCTGCCCTG
TCCGGAGCTGCCAGCACAGAACGCAAAATTAAAGGGGGGGCCCTACCCCTGAGTCAAGGCCCTAAGTGA
TATTACGGACTGGCGCTGTTTACACGTCGACTGGGAAACCCCTGGCTTACCCAACTTAATGCCCTGAGCAC
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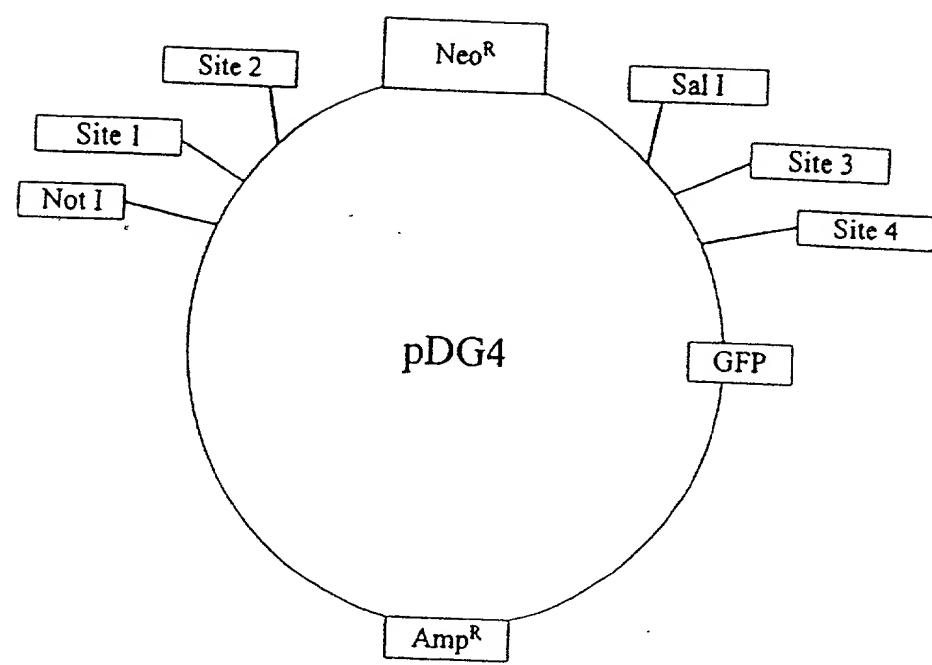


FIGURE 3A

FIGURE 3B

pDG4:

GT₁₁TAATGTAATCAATTACGGGTCAATTAGTTCATAGCCATATATGGAGTCCGGCTTACATAACTTACGGTAAATGG
CCCGCCTGGCTGACGCCAACGACCCCCGCCATTGACGTCAATAATGACGTATGTTCCATAGTAACGCCAATAGGG
CTTCCAATGACGTCAATGGGTGGAGTATTACGGTAAACTG₁₂CCACTTGGCAGTACATCAAGTGTATCATATGCCAAGT
ACGCCCCCTATTGACGTCAATGACGGAAAATGGGCCCTGGCATTAAAGCCAGTACATGACCTATGGGACTTCTAC
TTGGCAGTACATCTACGTATTAGTACATCGTATTACCATGGTATGGTGTGGCAGTACATCAATGGCGTGGGATAGC
GGTTTGACTCACGGGATTTCAGTCTCCACCCATTGACGTCAATGGAGTTTGGCACC₁₃AAATCAACGGGAC
TTTCCAAAATGTCGTAACAACCTGGCCATTGACGAAATGGCGGTAGGGTGTACGGTGGGAGGTCTATATAAGCAG
AGCTGGTTAGTGAACCGTCAAGTCCGCTAGGGTACCGGTGCCACATGGTGAGCAAGGGCGAGGAGCTGTTACCGG
GGTGGTGGCCATCTGGTCGAGCTGGACGGCAGTAAACGCCACAAGTCAAGCTGTCGGCGAGGGCGAGGGCGATG
CCACCTACGGCAAGCTACCCGCAAGTTCATGCAACACCGCAAGTGGCCCTGGCCACCCCTGTGACCC
CTGACCTACGGCGTGCAGTGTCTAGCCGCTACCCGACCATGAAAGCAGCAGACTTCTCAAGTCTCGCCATGCCGA
AGGCTACGTCAGGAGCGCACCATCTTCTCAAGGACGAGGCAACTACAAGACCCGCGCAGGTGAAGTTCGAGGGG
ACACCCCTGGTGAACCGCATCGAGCTGAAGGGCATGACTTCAAGGAGGACGGCAACATCTGGGACAAGCTGGAGTAC
AACTACAACAGCCACAAGCTATATCATGGCGACAAGCAGAAGAACGGCATCAAGGTGAACTCAAGATCCGCCACAA
CATCGAGGACGGCAGCGTGCAGCTCGCCGACCATACCGAGAGAACCCCCATGGCAGGGCCCTGTGCTGCTGCCG
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CATATACTAGCCATACACATTGAGGTTTACTTGTGTTAAACCTCCACACCTCCCTGAACTGAAACATA
AAATGAATGCAATTGTTGTTAACTTGTGTTATTGAGCTTAAATGGTTACAAATAAGCAATAGCATCACAAATTTC
ACAATAAAAGCATTTTCTACTGCAATTGTTGTTGTTCAACTCTAATGTATCTTAAACCGGAACTACCGTCA
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GAGACAATAACCTGATAAAATGCTTCAATAATATTGAAAAGGAAGACTATGAGTATTCAACATTCCGCTGCTGCCCTA
TTCCCTTTTGCGGCATTGCTTCTGTTGCTACCCAGAAAAGCTGGTAAAGTAAAAGATGCTGAAGATCAG
TTGGGTGACAGTGGGTTACATCGAAGTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTCCGCCCCGAAGAACGTT
TCCAATGATGAGCATTAAAGTCTGCTATGTGGCGGTATTATCCCTGTTGACGCCGGCAAGAGCAACTCCGTC
GCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCAGAAAAGCATCTACGGATGGCATGACAGTA
AGAGAATTATGCACTGCTGCCATAACCATGAGTGATAACACTGCCAACCTACTTCTGACACGATCGGAGGACCGA
GGAGCTAACCGCTTTTGCAACACATGGGGATCATGTAACCTGCCCTGATGTTGGAACCGGAGCTGAATGAAGCCA
TACCAAAACGACGAGCGTGACACCAGATGCCCTGAGCAACACGTTGCGAACACTATTAAACTGGCGAACACTATT
ACTCTAGCTTCCCGCAACAAATTAAATAGACTGGATGGAGGCGGAAAGTGTGAGCAGGACACTTCTGCGCTCGGCCCTCC
GGCTGCTGGTTATTGCTGATAATCTGGAGCCGGTGGCTGGCTGGGTCTCGGGTATCTGAGCAGCATGGGCCAGT
GTAAGGCCCTCCCGTACTGCTAGTTATCACGACGGGAGCTAGGGCAACTATGGTGAACGAAATAGACGATCGCTGAG
ATAGGTGCTCACTGATTAAGCATTGGTAACTGTCAGGCAACTGTTACTCATATAACTTAAAGTGTATTACCCGGTT
GATAATCAGAAAAGCCCAAAACAGGAAGATGTATAAGCAAAATTAAATTGAAACGTTAATATTGTTAAAATT
CGCTTAAATTGTTAAATCAGCTCATTTTAACCAATAGGCCAACTGGCATAACCTCCCTATAATCAAAGAAT
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GGTGTGCAAAACAAAAAACCCACCGCTACAGCGGTGGTTTGTGCGGATCAAGACTACCACCTTTCCGGAAG
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AACGCCAGCAACCGCCCTTTACGGTCTCTGCTTGTGCTCACATGTAATGCTAGTTAGCTCACT
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GGAAAAGCTATGACCATGTTACGCCAAAGCTACGTAATACGACTCACTAGCGGCCGCTTAAACAATGCTCTCT
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ATTCTGCAAGGATTGGCCCTGGGGCAGCGGCAATAGCAGCTTGTCTCCCTGGGCTTTCCCAAGGAGTCTGGAGCAT
GCGCTTACGCCGCTGGCACTGGCGTACACAAGTGGCCTCTGGCTCGCACACATTCCACATCCACCGGTAGCG
CCAACCGCTCCGTTTGGGCCCCCTGGCGCACCTCTACTCTCCCTAGTCAGGAAGTCCCGGGGCCCCGCCCCGC
AGCTCGCGTGTGCAAGGAGCTGACAAATGGAAGTAGCACGTCGACTAGTCTGTCAGATGGACAGCACCGCTGAGCAA
TGGAGCGGTAGGGCTTGGGGCAGCGGCAATAGCAGCTTGTCTCCCTGGGCTAGAGGCTGGGAGGG
TGGGTCCGGGGCGGGCTCAGGGGGGGCTCAGGGGGGGGGCGAGGGGGGGGGGCTGGGCTAGAGGCCCCGATTCTGCAC
GCTTCAAAAGGGCACGTCGCTGGCCCTCTGGGCCCCCTGGCGCACCTCTACTCTCCCTAGTCAGGAAGTCCCGGGGCCCCG
GCCATTGAAACAGATGGATTGCAAGCAGGTTCTGGCCCTGGGCTGGGAGGGTATTGGGTATGACTGGGCAACACA
GACAATCGGCTCTGATGCGCCCTGCTGAGGGAGGGAGGGCTATGTCAGGCCACGACGGGCTTCTGGCAGCTGT
CCGGTGCCTGAATGAACTGCAAGGAGGGAGGGAGGGCTATGTCAGGCCACGACGGGCTTCTGGCAGCTGT
CTCGACGTTGCACTGAAAGCGGAAAGGGACTGGCTGCTATTGGCGAAGTGGGGGGAGGATCTCTGTCATCTCACCT

TGCTCTGCCGAGAAAGTATCCATCATGGCTATGCAATGCCGGCTGCATACGGCTGATCCGGTACCTGCCATTG
ACCACCAAGCGAAACATCGCATCGAGCGAGCACGTACTCGATGGAAGCCGGCTTGTGATCAGGATGATCTGGACGAA
GAGCATCAGGGGCTCGCGCAGCGAAGCTGTCGCCAGGCTCAAGGCGCGATGCCGACGGCGATGATCTCGTCGTGAC
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TGGCGACCGCTATCAGGACATAGCGTTGGCTACCCGTATTTGCTGAAGAGCTTGGCGGGAATGGCTGACCGCTTC
CTCGTGTCTTACGGTATGCCGCTCCGATTGCGAGCGATGCCCTCTATGCCCTTGTGACGAGTTCTCTGAGGGGA
TCGATCCGTCCTGTAAGTCTGAGAAATTGATGATCTTAAACAATAAGATGTCACATAAAATGGAAGTTTCTGT
CATACTTTGTTAAGAAGGGTGAAGAACAGAGTACCTACATTGATGGAAGGATTGGAGCTACGGGGTGGGGTGGGT
GGGATTAGATAATGCCGCTTTACTGAAGGCTTTACTATTGCTTATGATAATGTTTCAATAGTTGGATATCATAA
TTAAACAAGCAAACCAAATTAAAGGCCAGCTCATCCTCCACTCATGATCTATAGATCTCTCGTGGGAT
CATTGTTTCTCTGATTCCCACCTTGTTCTAAGTACTGTGTTCCAAATGTCAGTTCATAGCCTGAAGAAC
GAGATCAGCAGCCTCTGTCACATACACTTCATTCTCAGTATTGTTGCAAGTCTAATCCATCAGAAGCTGACTC
TAGATCTGGATCCGGCAGCTAGGCCGTCGACCTCGAGTGAATCAGGTACCAAGGTCTCGCTCTGTCGTTGAGCTG
ACGACACAGGACACGCAAATTAAATTAAAGGCCGGCCGTACCCCTAGTCAGGCTTAAGTGAATGTCGTTACCGACTGG
CCGTGTTTACACGTCGTACTGGAAAACCCCTGGCGTACCCAACTTAATGCCCTTGCAAGCACATCCCCCTTCGCC
ACCTGGCGTAATAGCGAAGAGGCCGACCGATGCCCTCCAAAGTTGCGCAGCCTGAATGGCGAATGGCGCTCGC
TTGGTAATAAAGCCGCTTGGCGGCTTTTTTTT

FIGURE 3B (Continuted)

Annealing site	Sequence	Sequence after digestion
1	5' tgtgctccctttggcttgcctccaa... 3' 3' acacgaggagaacccgaacgaaaggtt... 5'	5' tgtgctccctttggcttgcctccaa... 3' 3' tt... 5'
2	5' ctggttcttgtctggcttggcccaa... 3' 3' gaccaagaacacgaccgaacccgggtt... 5'	5' ctggttcttgtctggcttggcccaa... 3' 3' tt... 5'
3	5' ggtccctcgctctgtgtcccggttggaa... 3' 3' ccaggaggcggagacacaggcaactt... 5'	5' ggtccctcgctctgtgtcccggttggaa... 3' 3' tt... 5'
4	5' tttgcgtgtcctgtgtcgtcgtcgaa... 3' 3' aaacgcacaggacacaggcagttt... 5'	5' tttgcgtgtcctgtgtcgtcgtcgaa... 3' 3' tt... 5'

FIGURE 4

Annealing site	Sequence	Sequence after digestion		
1	5' AAtgtgctccttggcttgcgtccgc 3'	5'	AA	3'
	3' Ttacacgaggaaaacggaaacgaaagg 5'	3'	Ttacacgaggaaaacggaaacgaaagg 5'	5'
2	5' AAActggttcttggcttggCCCGC 3'	5'	AA	3'
	3' Ttgaccaagaacacgacggaaaccggg 5'	3'	Ttgaccaagaacacgacggaaaccggg 5'	5'
3	5' AAGgtccctcgctctgtgtccgttgAGCT 3'	5'	AA	3'
	3' Ttccaggaggcgagacacaggcaac 5'	3'	Ttccaggaggcgagacacaggcaac 5'	5'
4	5' AAttggcggttccctgtcgctGAGCT 3'	5'	AA	3'
	3' Ttaaacggcacaggacacaggcagc 5'	3'	Ttaaacggcacaggacacaggcagc 5'	5'

FIGURE 5

FIGURE 6

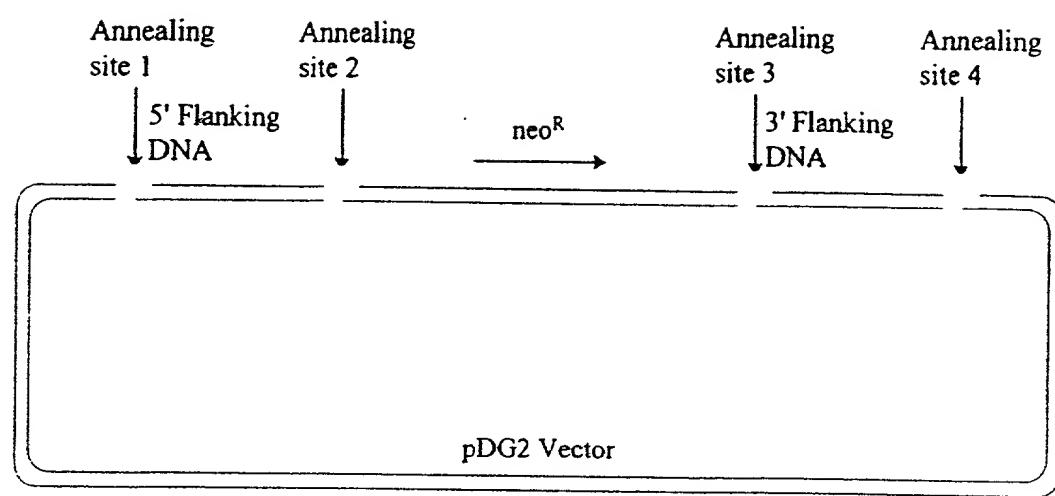
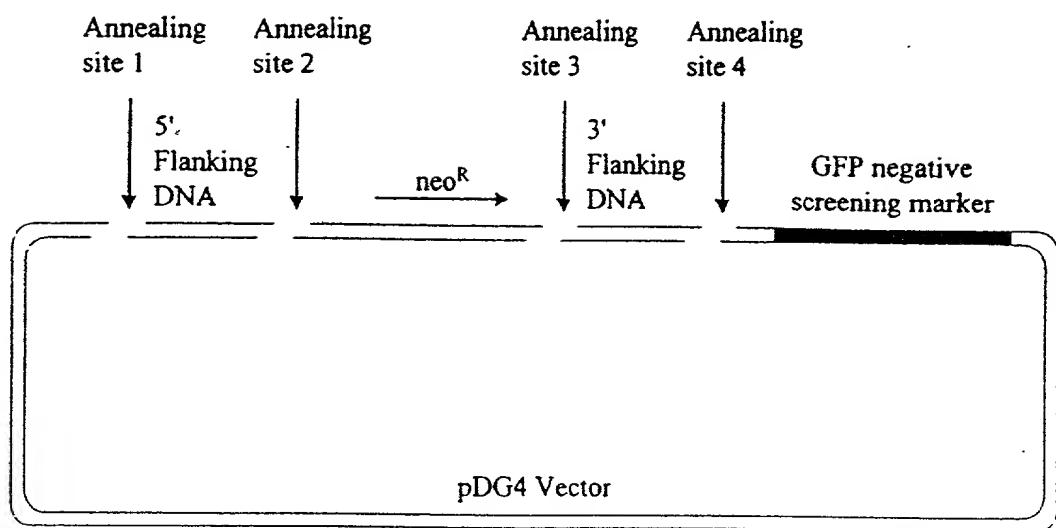


FIGURE 7



TCGGTTGGGCCAGCAACTCTAGCAAGCAGGCTACCCCTAGGACCATCCATATCGATGAGCTCTACAG
TGGCTGCCTCCACTATGCCTGTCTGTGGCCGCCCTCAAGAAGGAGTCTCCAGGTAGATGGGCCCTGG
AGAGGATCCAACAGGTGTGGCCGCCCTCGCTCCAGTGGCAGTGTGGGACAGCAGCAGTGGAAACAT
TATGGCATCTATGCCTGCAATGGCTGCAGTGGCTTCAAGAGGAGTGTGAGAAGGAGGCTCATCTACA
GGTCCAAGTCGGGCAGGGATGTGCCAGTGGATAAGGCCATCGCAATCAGTGCAGGCCCTGCCGGCT
GAAGAAGTCTTACAAGCAGGCATGAACCAAGATGCTGTGCAGAATGAGGCCAACCTCGGAGCATGGCT
CAGGTTCCACCTGGATGCCATGGAAACAGGCAGTGAACCCGATCAGAACCAAGTGGTAGCCTCTGCC
TGGCAGGGCCAGTCCCCGGGGCCACGTCTGTCTGCACCCAGAGGCCATGGCCACCAACTTATGGC
CAGCCTTATCACCAGGAAACTTGTCTAAACTGGAGCCAGAGGACGCTGAAGAGAATATTGATGTCACC
AGCAATGACCCCCAGTTCCCCGATCCCCCTGCAGTCTGGATGGCATCCATGAGACATCTGCTGCC
TCTTCATGGCTGTCAAATGGGCCAAAACTTGCCTGTGTTTCAACCTGCCTTCCGGACCAGGTGAT
CTTGCTGGAAGAGGCATGGAATGAGCTTTCTCTTGAGCCATACAGTGGTCTGTGCCAGTGCAG
TGCCCAGTGCCTGCCACCCTGAGGCGTCCGGCAGCTCTCAGGGCAGGCTGGCCTGGCCAGTGCAG
CGCGCTTCCCTGCAGGAAACCATCTCCGGTCCGGAGCTCTGCAGTGGATCCCACAGAGTTGCCTGC
GAAGGCCCTGGTCTCTCAAAACCTGAAACACGAGGCTGAAGGATCTGAGCACGTGGAGGCTTGAG
GACCAGTCCCAGGTGATGCTAAGCCAGCATAGCAAGGCTCACCAACCCAGCCAGCCTGTGAGGTTGG
AATTGCTCCCTGCTCCATCTTGAGGTTCTCACGGCTGAGCGCATGGCTTCTCTTCAGAAA
GACCATAGGAAACACTCCGATGGAGAAGCTCCTGTGACATGGCTTCTCTTCAGGCTTCTCTTCAG
GTCCACAGGCACCCAGGGGGCAGCACATCTAGAAGCTAAATAGTCCCTGCCTTCTCAGCCAGTAAT
TCCACATTCAAGGTTCTACCTAGCAGAAATTCTCCAAATATATTATTGGCATATTGCCATC
CTAACCTTAATACCCCTAACCTCTGCTTGGCAGTAGAATGCATGGATGCCTGTTATATTCAAG
ACAGCTTGGCAAAAAAAAAAAAAAA
(SEQ ID NO: 19)

Targeting Vector (5' arm; 200 bp flanking neo insert):

AGACTGAAAGACAGACAGACAGACAGACAGACAGAGGGTTAAAGATGGATGCATGGTTGGGCCAGCAACT
TCTAGCAAGCAGGCTACCCCTAGGACCATCCATATCGATGAGCTCTACAGTGGCTGCCTCCACTATG
CCTGTGTCTGTGGCCGCCCTCAAGAAGGAGTCTCCAGGTAGATGGGCCCTGGAGAGGATCCAAC
(SEQ ID NO: 20)

Targeting Vector (3' arm; 200 bp flanking neo insert):

CTCCAGTGCCAGTGTTGGGGACAGCAGCAGCAGTGGGAAACATTATGGCATCTATGCCTGCAATGGCTG
CAGTGGCTTCTCAAGAGGAGTGTGAGAAGGAGGCTCATCTACAGGTGCCACAGCTCTGCCGGCTG
CCCCGGTGTGCCTAGCACGGGTGGAGGGCGTTCAAGGGAAAGCGGAAGACGAGGACCAAGGGCAAACA
(SEQ ID NO: 21)

FIG. 8